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14. ABSTRACT

Mouse models suggest that chronic stress promotes ovarian tumorigenesis, but the relationship between stress and ovarian cancer has never been evaluated in humans. Over the last year of the grant, we published an analysis demonstrating that exposure to chronic stress leads to tumors that express the beta-2 adrenergic receptor, the signaling pathway identified in mouse models. We have also made progress developing a metabolomic signature of post-traumatic stress disorder (PTSD), a sentinel chronic stress condition. Overall, our continuing work on the role of stress in ovarian cancer development indicates that chronic stress may increase risk of developing ovarian cancer.

15. SUBJECT TERMS
ovarian cancer, psychosocial stress, depression, anxiety, social support, metabolomics

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INTRODUCTION

The objective of this Ovarian Cancer Academy award is to evaluate the role of psychosocial stress in ovarian cancer risk through multiple measures of stress. This study is being conducted in the Nurses' Health Studies (NHS and NHSII), two large prospective cohorts with about 1200 ovarian cancer cases between the two studies. In these two study populations, we have repeated questionnaires in which we have queried psychosocial stress, as well as pre-diagnostic blood specimens on 350 cases, and tissue blocks on 250 cases. The first specific aim of this application is to examine whether self-reported stress exposures (depressive symptoms, phobic anxiety, social support, job strain, care-giving stress) are associated with ovarian cancer risk. Also, in this aim, we will evaluate whether any associations are stronger for tumors which express the β_2 adrenergic receptors, as studies in mouse models have suggested that β_2 adrenergic receptor activation drives ovarian tumorigenesis. In the second aim, we will use metabolomic profiling of women with and without post-traumatic stress disorder (PTSD) to derive a signature of chronic stress and then apply that metabolomic stress signature to study women with and without ovarian cancer. As secondary aims, we will evaluate whether stress is more strongly associated with more aggressive tumors (defined by how quickly fatal the tumors are, and by likely tubal vs. ovarian origin) and will leverage the metabolomics data to query other potential pathways of interest, including lipid dysregulation.

KEYWORDS

Ovarian cancer, psychosocial stress, anxiety, depression, social support, metabolomics

ACCOMPLISHMENTS

The major goals of this project were 1) to evaluate whether self-reported psychosocial stress is associated with ovarian cancer, particularly for tumors that express the β2-adrenergic receptor (SOW task 1); 2) to develop a metabolomic signature of chronic stress (SOW task 2); 3) to evaluate whether the PTSD metabolomic signature described in Task 2 is associated with risk of ovarian cancer (SOW task 3); to evaluate whether metabolomic biomarkers of lipid disregulation are associated with ovarian cancer risk (SOW task 4); and 5) career development (SOW task 5).

For task 1, tasks 1a-1f were completed in prior grant periods. In the current grant period, Dr. Poole and her post-doctoral fellow published (or submitted) their analyses examining whether stress-related exposures as well as known ovarian cancer risk factors are differentially associated with tumors that express the β2-adrenergic receptor (task 1g). As hypothesized, many stress exposures (e.g., depression, phobic anxiety) seem to only be associated with increased risk of tumors that express the β2-adrenergic receptor, although the numbers are small and not all stress exposures seem to increase risk of β2-adrenergic receptor positive tumors. Additional manuscripts evaluating the association of other stress exposures with risk of ovarian cancer have been published or submitted over the last grant year. For example, our manuscript on depression in ovarian cancer risk was published in Gynecologic Oncology. Our analysis of phobic anxiety and ovarian cancer risk was published in Cancer Causes and Control, and manuscripts on job strain and caregiver burden are submitted (See preliminary results in Table 2). For these analyses, Dr. Poole is mentored a post-doctoral fellow (Claudia Trudel-Fitzgerald) and a doctoral student (Mollie Barnard), respectively. As noted in the prior progress report, completion of task 1 was somewhat delayed due to complications in the β2-adrenergic receptor. However, due to the delays in task 1, we started task 3

Table 1. Differences in stress exposure associations (RR; 95% CI) by tumor β2-adrenergic receptor expression

	Tumor β2-adrenergic receptor expression		
	Positive	Negative	P-het
Depression	2.33 (0.85, 6.35)	1.14 (0.65, 2.01)	0.23
Phobic anxiety	2.60 (1.16, 5.87)	1.16 (0.81, 1.66)	0.07
Caregiver stress	0.95 (0.84, 1.08)	0.99 (0.95, 1.03)	0.49
High job demand	0.81 (0.26, 2.57)	0.70 (0.44, 1.13)	0.82
High job control	2.01 (0.63, 6.39)	1.13 (0.70, 1.81)	0.36

Relative risk (RR) and 95% confidence interval (CI) adjusting for age, known ovarian cancer risk factors, and cohort (NHS vs. NHSII)

Table 2. Associations of caregiver burden and job strain on ovarian cancer risk.

Stress measure	Comparison	RR (95% CI)
Caregiver burden	≥15 hours/week of caregiving vs. none	0.86 (0.67, 1.11)
Job strain	Job insecurity	1.28 (1.01,1.61)

earlier than expected.

In task 2, Dr. Poole completed task 2a in prior grant periods, as noted on the prior progress report. WE have completed task 2b (metabolomics assays) in Dr. Clish's lab. Dr. Poole is mentoring her post-doctoral fellow, Oana Zeleznik to accomplish Tasks 3c-d. Dr. Zeleznik has completed preliminary analyses of the association of metabolites with PTSD. We assayed 239 known and 1996 unknown metabolites in 100 women with PTSD, 100 women with no trauma exposure, and 25 women exposed to trauma, but who did not develop PTSD. We identified 78 metabolites associated with PTSD at a false discovery rate (FDR) <0.20. Known metabolites associated with PTSD included glutamate, serotonin, tryptophan, C16:0 ceramide, C34:2 diacylglycerol (DAG), C34:3 DAG, C36:4 DAG, and C38:3 PE plasmalogen. Further analyses, such as clustering and dimension reduction, to validate and enhance the current PTSD metabolomic signature are ongoing. We expect to completed Task 3e (manuscript preparation) in this grant period.

For task 3; we completed 3a (selection of samples) in prior grant periods. In this period, we completed the metabolomics assays (3b) and Drs. Poole and Zeleznik are currently working to perform data analyses (Tasks 3c-d). We anticipate completing these analyses on schedule.

Task 4 has not yet begun.

For task 5 (career development), Dr. Poole meets weekly with Dr. Tworoger (her Academy mentor) and monthly with Dr. Kubzansky (a co-mentor on this project). Dr. Poole leads bi-weekly meetings of our internal Ovarian Cancer Analysis Group (OCAG) with her mentor, Dr. Tworoger, as well as with Dr. Katie Terry, a fellow Ovarian Cancer Academy Early Career Investigator. Dr. Poole has also attended the regular bi-monthly meetings of the stress and cancer working group. Regarding scientific conferences, Dr. Poole attended the AACR/Rivkin Special Conference on Ovarian Cancer in October 2015, the Dana Farber/Harvard Cancer Center (DF/HCC) annual breast and gynecologic cancer retreat in March, 2016, the annual meeting of the Ovarian Cancer Association Consortium in April, 2016, the Society for Epidemiologic Research (SER) annual meeting in June, 2016, the DoD Ovarian Cancer Academy meeting in September 2016, and the Rivkin Center's Ovarian Cancer symposium in September 2016 (held in conjunction with the DoD academy meeting).

In addition to the career development tasks outlined in the statement of work, Dr. Poole continues her leadership role as the Associate Director for omics data for the Harvard Cohorts (including the Nurses' Health Studies) and as director of the Channing Division of Network Medicine (CDNM)'s Junior Faculty group, which meets bi-weekly to discuss career challenges, present grant aims and receive feedback, and invites outside speakers to provide career advice. Dr. Poole is also a peer mentor to three post-doctoral fellows working in the CDNM.

Results from the ongoing research in the role of stress in ovarian cancer have been communicated to the scientific community in various ways. Dr. Poole has presented on her work at local meetings (the DF/HCC annual breast and gynecologic cancer retreat), the Society for Epidemiologic Research, and the Rivkin Symposium on ovarian cancer. Her students and post-docs have also presented posters at local and international meetings. For example, Dr. Zeleznik will present a poster on the PTSD metabolomics signature in November 2016 at a metabolomics meeting.

In the next reporting period, Dr. Poole will work with her mentors to complete the metabolomic signature of stress (SOW task 2) and to apply it in the nested case-control study of ovarian cancer (SOW task 3). She will submit all manuscripts planned for SOW tasks 2 and 3, working with students and post-doctoral fellows to complete these projects.

IMPACT

The major impact of this project to date is the evidence that self-reported psychosocial stress seems to be related to developing ovarian cancer, the first demonstration of this in humans. While this adds to the evidence that stress management is important for long-term health, validation in other studies is required. The upcoming work on metabolomics will help elucidate the biologic underpinnings linking stress to ovarian cancer risk.

CHANGES/PROBLEMS

Nothing to Report

PRODUCTS

Publications, conference papers, and presentations

Journal publications.

1. Huang T, Poole EM, Okereke OI, Kubzansky LD, Eliassen AH, Sood AK, Wang M, Tworoger SS. Depression and risk of epithelial ovarian cancer: Results from two large prospective cohort studies. Gynecol Oncol. 2015 Dec;139(3):481-6.
2. Huang T, Poole EM, Eliassen AH, Okereke OI, Kubzansky LD, Sood AK, Forman JP, Tworoger SS. Hypertension, use of antihypertensive medications, and risk of epithelial ovarian cancer. International journal of cancer. 2016; 139(2):291-9.
3. Poole EM, Kubzansky LD, Sood AK, Okereke OI, Tworoger SS. A prospective study of phobic anxiety, risk of ovarian cancer, and survival among patients. Cancer causes & control : CCC. 2016; 27(5):661-8.
4. Huang T, Tworoger SS, Hecht JL, Rice MS, Sood AK, Kubzansky LD, Poole EM. Association of ovarian tumor β2-adrenergic receptor status with ovarian cancer risk factors and survival. Cancer Epidemiol Biomarkers Prev. 2016, epub.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name:	Elizabeth Poole
Project role:	PI
Research Identifier	ORCID: 0000-0002-4680-4587
Nearest person month worked	7
Contribution to Project	PI – coordinated all analyses and assays
Funding Support	

Name:	Shelley Tworoger
Project role:	Mentor/co-investigator
Research Identifier	ORCID: 0000-0002-6986-7046
Nearest person month worked	1
Contribution to Project	Project mentor – provided guidance and feedback on all tasks; met weekly with Dr. Poole
Funding Support	

Name:	Tianyi Huang
Project role:	Post-doctoral fellow
Research Identifier	ORCID: 0000-0001-8420-9167
Nearest person month worked	1
Contribution to Project	Performed analyses of β2-adrenergic receptor
Funding Support	US National Cancer Institute

Name:	Claudia Trudel-Fitzgerald
Project role:	Post-doctoral fellow
Research Identifier	ORCID: 0000-0001-9989-4259
Nearest person month worked	1
Contribution to Project	Performed analyses of job strain and risk of ovarian cancer
Funding Support	Canadian National Cancer Institute

Name:	Mollie Barnard
Project role:	Doctoral student
Research Identifier	N/A

Nearest person month worked	1
Contribution to Project	Performed analyses of caregiver burden and risk of ovarian cancer
Funding Support	US National Cancer Institute
Name:	Oana Zeleznik
Project role:	Post-doctoral fellow
Research Identifier	ORCID: 0000-0002-8705-1163
Nearest person month worked	6
Contribution to Project	Developed metabolomics signature of PTSD
Funding Support	US National Cancer Institute

No changes in active support to be reported.

No other organizations were involved as partners.